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09/125,751	10/30/98	FODSTAD	4885.55USWO

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EXAMINER	
UNGAR, S	
ART UNIT	PAPER NUMBER
1642	20

DATE MAILED: 08/08/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/125,751	Fodstad et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 20, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3, 6-8, and 13-25* is/are pending in the application.

4a) Of the above, claim(s) *13* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3, 6-8, and 14-25* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

1. The request filed on January 30, 2001 (Paper No. 18) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/125,751 is acceptable and a CPA has been established. An action on the CPA follows.

2 The amendment filed on January 20, 2001 (Paper No. 19) is acknowledged and has been entered. Claim 1 has been amended and new claims 15-25 have been added. Claims 1, 3, 6-8 and 14-25 are pending and currently under examination.

3. The Restriction Requirement of November 9, 1999 (Paper No. 7) and the Response to the Restriction Requirement submitted January 3, 2000 (Paper No.11) wherein Applicant elected the species of MUC1 for examination is noted. The restriction requirement is maintained in this CPA. Further, it is noted in Amendment C filed August 14, 2000 (Paper No. 15), that claim 3 was amended to insert the phrase "antigen binding". However, it is also noted that the amendment was improper and was inadvertently entered because in the same amendment, it is has been found that the antibody claimed in claim 3 was switched from BM7 to 595A6 without either brackets around the originally filed BM7 or the underlining of 595A6. Because antibody 595A6 is not mentioned in the specification as originally filed and in the interests of compact prosecution, it is assumed for examination purposes that a typographical error occurred in Paper No. 15 which was carried on to the Preliminary amendment, Paper No. 19 and that the antibody under consideration is meant by Applicant to be antibody BM7 which is an anti-MUC-1 antibody, especially since Applicant's arguments in Paper No. 19, on page 6, are specifically

drawn to the rejection of claim 3 and BM7 in particular. Appropriate amendment of claims 3 and newly added 16 to recite the BM7 antibody is required.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

6. Claims 1, 3 and 6-8 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 13, Section 6 pages 3-6 and in Paper No. 17, Section 4, pages 2-3.

Applicant argues that (a) the probability of successfully killing malignant cells *in vivo* using the treatment established in *vitro* is very high due to the high specificity of the antibodies, the effectiveness of the combined immunotoxin approach, the low toxicity of the combined approach, previous data indicating clinical localization of Moc 31, (b) it is generally accepted that even though the transition from *ex vivo* to *in vivo* is complex, this is the only accepted method for testing medicaments. Thus it is a general opinion in the art that it is not possible to test the effect of cancer medication without a basis in *ex vivo* experiments as has been and is being done in large governmental and company screening programs. The arguments have been considered but have not been found persuasive because (a') and (b') as previously disclosed, Applicant has speculated, without *in vivo* experimentation, that due to the high specific activity of the disclosed immunotoxins *in vitro* it seems possible to administer the mixture for *in vivo* treatment of patients suffering from different types of carcinoma. Given what is understood in the art, no

one of skill in the art would accept Applicant's hypothesis that it would be more likely than not that the invention would function as claimed *in vivo* in the absence of a demonstration of the efficacy of the method in an appropriate animal model. Further, as drawn to the other parameters, that is the effectiveness of combination, low toxicity and clinical localization, the arguments are not persuasive for the reasons previously set forth. In addition, these characteristics have been demonstrated *in vitro* only for a single set of specific immunotoxins which are not specifically claimed. Even if *in vitro* data were convincing, this single example would not be sufficient to enable the broadly claimed invention. Finally, Applicant submitted the catalog page for MOC-31 from Zymed Laboratories with Paper No. 19. Zymed Laboratories specifically states that the intended use of the antibody if **"FOR RESEARCH USE ONLY"** (emphasis added). The claims are drawn to treatment and not to research. Applicant's arguments have not been found persuasive and the rejection is maintained.

7. Claim 3 remains rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 13, Section 7, pages 6-9 and in Paper No. 16, Section 5, page 4.

Since it is assumed for examination purposes that a typographical error occurred and that BM7 is intended to be claimed, Applicant's arguments are relevant to the instant rejection.

Applicant argues that antibody BM7 can be obtained from MEDAC GmBH and Applicant includes a description of antibody BM7 from the MEDAC home page. The argument has been considered but has not been found persuasive since

no evidence has been submitted showing that the antibody is commercially available. Applicant is invited to submit objective evidence demonstrating that the antibody is commercially available, for example a catalogue page as submitted for MOC31. Applicant's arguments have not been found persuasive and the rejection is maintained.

8. Claims 1, 3, 6-8 and 14 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in paper No. 13, Sections 8(c and g) pages 10-11 and in Paper No. 16, Section 6, pages 4-5.

Because Applicant did not distinctly and specifically point out the supposed errors in the rejection, the rejection is maintained.

Claim Rejections - 35 USC § 103

9. Claims 1 and 14 remain rejected under 35 USC 103 and newly added claims 21 and 25 are rejected under 35 USC 103, for the reasons previously set forth in Paper No. 13, Section 10, pages 12-15 and in Paper No. 16, Section 7, pages 5-7.

Applicant argues that none of the references, either alone or in combination teach or suggest the present invention since (a) the MOC31 antibody is an antibody that is specific for the GA733.1 antigen and the antibody taught by the '254 patent is non-specific as compared to MOC31, (b) the essential features and requirements of the claimed invention are not met by the references because the present method requires that (i) the correct antibody is bound to the correct antigen and antigen epitope, (ii) the antibodies must be connected to the optimal toxin in order to get optimal cellular internalization, (iii) all of the cited publications concern *ex vivo* methods and don't show how these methods will work in *vivo*, (iv) the combination

of the cited publications did not suggest if the binding of the toxin to antibody destroyed the antigen-antibody binding capacity. This had to be tested by experimentation.

The arguments have been considered but have not been found persuasive because (a') neither claim 1 nor claim 14 is drawn to MOC31 antibody. Further the antibody taught by the '254 is clearly specific to breast cancer cells. Applicant is reminded that the specificity of an antibody is drawn only to its epitope binding properties. The '254 patent specifically teaches that Mab GA733 binds to breast tumor carcinoma, (b')(i') US Patent No. 5,185,254 clearly teaches Mab GA733 which binds to breast tumor carcinoma cells, (ii') the claims are drawn to the toxin PE, Bjorn et al clearly teaches that monoclonal antibodies conjugated to PE kill breast cancer cells *in vitro*, (iii') claim as broadly written include ex *vivo* methods and claim 14 is specific to an *ex vivo* method, (iv') the conjugation of toxins to monoclonal antibodies was conventional in the art at the time the invention was made. Further, Bjorn et al specifically teaches the successful conjugation of PE to monoclonal antibodies and their ability to kill breast cancer cells *in vitro*. The prior art references provide not only the means but also the motivation to make and use the claimed invention. The arguments have not been found persuasive and the rejection is maintained.

Although the prior art references do not specifically teach the newly added limitation of low toxicity to CD34+ cells, the claimed method appears to be the same as the method of the combined prior art, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the

factual evidence needed in order to establish that the product of the method of the combined prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from that taught by the combined prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

New Grounds of Objection

10. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter, see 37 CAR 1.75(d)(1) and MPEP 608.01(o). Claims 1, 3, 6-8 and 14 are drawn to toxin fragments. However, the claims must find support in the specification, which the instant claims 1, 3, 6-8 and 14 do not. The claims as filed in the original specification are part of the disclosure and therefore, if an application as originally filed contains a claim disclosing material not disclosed in the remainder of the specification, the applicant may amend the specification to include the claimed subject matter. In re Benno, 768 F.2d 1340, 226 USPQ 683 (Fed. Cir. 1985). Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

11. Although it is assumed for examination purposes that a typographical error has occurred and that claims 3 and 16 are meant by Applicant to be drawn to Mab BM7, Claims 3 and 16 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The

limitation of "595A6 antibody" recited in claims 3 and 16 has no clear support in the specification and the claims as originally filed. A review of the specification did not reveal any mention of 595A6 antibody. The subject matter claimed in claims 3 and 16 broadens the scope of the invention as originally disclosed in the specification.

12. Although it is assumed for examination purposes that a typographical error has occurred and that claims 3 and 16 are meant by Applicant to be drawn to Mab BM7, the specification is objected to and claims 3 and 16 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claim is drawn to monoclonal antibody 595A6 conjugated to a toxin.

It is unclear if cell lines which produce antibodies having the exact structural and chemical identity of 595A6 are known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a hybridoma cell line producing monoclonal antibody 595A6 it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species, MOC31 and BM7. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant has not disclosed the deposit of hybridoma cell lines that would reproduce the antibody species 595A6.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement

is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

13. Claims 15-21 and 25 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitations of "at least two immunotoxins" recited in claim 15 and "two or more immunotoxins" recited in claim 21 have no clear support in the specification and the claims as originally filed. A review of the specification discloses support for selective purging of a cell population for target cells by exposing the cell population to a combination of two immunotoxins (p. 1, lines 1-2), a combination of two antibodies, each conjugated to PE (p. 11, line 13). There is neither a suggestion of nor guidance on using more than two immunotoxins. Further, the specification specifically teaches away from using more than two immunotoxins in the discussion on page 6, lines 26-36. The subject matter claimed in claims 15-21 and 25 broadens the scope of the invention as originally disclosed in the specification.

14. Claims 15-20 and 22-24 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "a method for killing malignant cells" recited in claims 15 and 22 has no clear support in the specification and the claims as originally filed. A review of the specification discloses support for killing breast cancer cells or other carcinoma cells (see claim 1 as originally filed), using antibodies that recognize an epithelial antigen coded for by GA733-2 gene which is expressed by most carcinoma cells and therefore can be used in all cases involving carcinomas and the other is directed to mucin which is slightly different from one carcinoma type to another (p. 11, lines 21-27). There is neither a suggestion of nor guidance on using the method on any cancer type other than breast cancer or other carcinomas with the

same antigens. The subject matter claimed in claims 15-20 and 22-24 broadens the scope of the invention as originally disclosed in the specification.

15. Claims 1, 3, 6-8, 14, 21 and 25 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "other carcinoma cells expressing target antigens" recited in claim 1 has no clear support in the specification and the claims as originally filed. A review of the specification discloses support for killing breast cancer cells or other carcinoma cells expressing the same antigens" (see claim 1 as originally filed) and a method of isolating stem cells for transplantation in such a way that the transplants should not contain any malignant cells (p. 3, lines 20-23). There is neither a suggestion of nor guidance on using the method with carcinomas that do not express the same antigens. The subject matter claimed in claims 1, 3, 6-8, 14, 21 and 25 broadens the scope of the invention as originally disclosed in the specification.

16. Claims 15-17 and 19-20 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "a cell population" recited in claim 15 has no clear support in the specification and the claims as originally filed. A review of the specification discloses support for a cell population comprising peripheral blood cells (p. 1, lines 5-10) or bone marrow cells (p. 1, line 26) and the object of the present invention which is to provide a method for purging of stem cell transplants (p. 4, lines 1-2). The subject matter claimed in claims 15-17 and 19-20 broadens the scope of the invention as originally disclosed in the specification.

17. If Applicant were able to overcome the rejections previously made and above, Claims 1, 3, 6-8 and 14-25 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing breast cancer or other carcinoma cells which comprise the EGP2 and MUC1 antigens, does not reasonably provide enablement for a method of killing other carcinoma cells which express target antigens/malignant cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to cancer cells that express target antigens/malignant cells. This includes any target antigens. The specification teaches the killing of breast cancer cells or other carcinoma cells expressing the same antigens" (see claim 1 as originally filed) and a method of isolating stem cells for transplantation in such a way that the transplants should not contain any malignant cells (p. 3, lines 20-23) and the claims are specifically drawn to immunotoxins that are directed against antigen EGP2 expressed by the gene GA733-2 and antigen expressed by MUC1 gene. One cannot extrapolate the teaching of the specification to the scope of the claims because it is clear that no one of skill in the art would believe that it would be more likely than not that the invention would function as claimed unless the immunotoxins are specific for the cells to be killed. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention

would function as broadly claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

18. If Applicant were able to overcome the rejections previously made and above, Claims 1, 3, 6-8, 21 and 25 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing breast cancer or other carcinoma cells wherein two immunotoxins are administered to the cell population or the cell population is contacted by two immunotoxins, does not reasonably provide enablement for a method of killing breast cancer or other carcinoma cells wherein the cell population is exposed to two immunotoxins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to the exposure of a cell population to two immunotoxins. This includes not only administration or combination of the immunotoxins with the cell population, but also the placement of the two immunotoxins near to, but not combined with the cell population. The specification teaches that the immunotoxins are combined with the cell population in order to kill and thus purge the malignant cells from the population. One cannot extrapolate the teaching of the specification to the scope of the claims because it is clear that no one of skill in the art would believe that it would be more likely than not that the invention would function as claimed unless the immunotoxins are combined with the cells to be killed. The specification provides insufficient guidance with regard to

these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the method would function as broadly claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

19. If Applicant were able to overcome the rejections set forth above, Claims 1, 3, 6-8, 14, 21 and 25 would still be rejected under 35 USC 112, first paragraph as the specification, while being enabling for the method claimed with PE as the toxin, does not reasonably provide enablement for said method wherein a fragment of PE is the toxin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The claims are drawn to fragments of PE. This includes any size fragment, whether it acts as a toxin or not. The specification teaches that the antibodies were conjugated to PE (p. 5, line 22). The two antibodies, each combined with PE killed malignant cells (p. 11, line 4). PE was obtained from Swiss Serum and Vaccine Institute and each antibody was conjugated to PE via a thioether bond (p. 15, lines 5-6). One cannot extrapolate the teaching of the specification to the scope of the claims because there is neither a suggestion of nor guidance on the use of the broadly claimed fragments of the toxin PE in the specification as originally filed. It is well known in the art that a fragment of a toxin, i.e two amino acids, would not act to "kill" cells. However, the claims as written read on fragments, whether active or not in the killing of the cancer cells. No one of skill in the art would believe that

it is more likely than not that a non-active fragment of PE would function as claimed. The specification provides insufficient guidance with regard to this issue and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

20. Claims 15-17 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *ex vivo* method for killing malignant cells in a cell population comprising nucleated cells in peripheral blood and bone marrow, does not reasonably provide enablement for an *ex vivo* method for killing malignant cells in a cell population. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The claims are drawn to *ex vivo* method for killing malignant cells in a cell population. This includes any cell population. The specification teaches cell populations comprising peripheral blood cells (p. 1, lines 5-10) or bone marrow cells (p. 1, line 26) and teaches that the object of the present invention is to provide a method for purging of stem cell transplants (p. 4, lines 1-2). The specification teaches the importance of autologous transplantation of circulating hematopoietic stem cells in the treatment of breast cancer and stresses that the current method was developed in order to produce a safe IT procedure to purge breast cancer cells from PBSCs and the specification demonstrates the efficient killing of all tumor cells

admixed with PBSCs without toxicity to the normal progenitor cells (p. 24). One cannot extrapolate the teaching of the specification to the scope of the claims because there is neither a suggestion of, mention of or guidance on any tissue that would be useful with this *ex vivo* method other than the tissues claimed in claim 1. It cannot be predicted from the teaching in the specification what other cell population could be used in this method. In the absence of such guidance or working examples that would provide such guidance, undue experimentation would be required to practice the claimed invention.

21. Claims 22-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons previously set forth in Paper No. 13, Section 6, pages 3-6 drawn to *in vivo* treatment and in Paper No. 16, Section 4, pages 2-3 and for the reasons set forth above..

Applicant's arguments drawn to the rejection of claims 1, 3 and 6-8 drawn to *in vivo* treatment are relevant to the instant rejection The arguments have been considered but have not been found persuasive for the reasons set forth above.

22. Claims 1, 3, 7, 15-21 and 25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 3 are indefinite because claim 1 recites the phrase "the cell population is exposed to". The claims are confusing because it is unclear whether the cell population is actually combined with the two immunotoxins, whether the

immunotoxins are administered or whether the two immunotoxins are simply placed in proximity to the cell population.

Although it is assumed for examination purposes that that claims 3 and 16 are meant by Applicant to recite Mab BM7, claims 3 and 16 are indefinite in the recitation of antibody 595A6 as the sole means of identifying the claimed antibody. The use of laboratory designations only to identify a particular antibody/cell line renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct hybridomas and antibodies. Amendment of the claims to include the depository accession number of the mAb or hybridoma is required, because deposit accession numbers are unique identifiers which unambiguously define a given hybridoma and/or monoclonal antibody.

Claim 7 is indefinite in the recitation of "especially in case of malignant spread to tissues such as bone and bone marrow" and "such as". The claim is confusing because it is not clear whether any other embodiments are meant to be included in the claim, for example, is the immunotoxin to be administered systemically if there is malignant spread to tissues other than bone and bone marrow? Further, the use of the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). The rejection may be obviated by amending the claim, for example, by deleting the phrase following the term "systemically".

Claims 15-20 are indefinite because claims 15 and 17 recite the phrases "obtaining the population of cells ex *vivo*" and "wherein the cell population is

obtained ex *vivo* from the patient". The claims are confusing because the term *ex vivo* is understood to mean outside of the body. It is not clear how the cell population can be obtained outside of the cancer patient when they must be obtained from the inside of the cancer patient.

Claims 21 and 25 are indefinite because they recite the phrase "low toxicity". The claims are indefinite because the term "low" is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 21 and 25 are indefinite because they recite the phrase "two or more immunotoxins" because there is no antecedent basis for the limitation in claim 1 from which they both depend.

23. Claims 23 and 25 are rejected under 35 USC 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim 23 is drawn to a patient, wherein the patient is a cancer patient. Claim 23 is dependent upon claim 22 which is drawn to a patient with malignant cells. Since the patient has malignant cells, the patient is by definition a cancer patient.

Claim 25 is a duplicate of claim 21 which is dependent upon claim 1. It is also dependent upon claim 1 and recites the same limitations as claim 21.

Claim Rejections - 35 USC § 103

24. Claims 15 and 17-20 are rejected under 35 USC 103, essentially for the reasons previously set forth in Paper No. 13, Section 10, pages 12-15 and in Paper No. 16, Section 7, pages 5-7.

The claims are drawn to a method to kill malignant cells in a cell population comprising contacting the cell population with a combination of two immunotoxins (its) wherein each is composed of an antibody and toxin, PE, wherein the antibodies are directed to epitopes on the antigen EGP2 and MUC-1, wherein the immunotoxins are administered *ex vivo*, wherein the cell population comprises peripheral blood cells or bone marrow cells, wherein the population comprises CD34+ cells, wherein the population is enriched or positively selected for CD34+ cells.

Applicant's arguments drawn to the rejection of Claims 1 and 14 are relevant to the instant rejection.

Applicant argues as set forth above. The arguments have been considered but have not been found persuasive for the reasons set forth above.

25. All other objections and rejections imposed in Paper No. 16 are withdrawn.

26. No claims allowed.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
August 6, 2001